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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/972,744	10/05/2001	Marcel P. Bruchez	5100-0702	4380

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EXAMINER	
DO, PENSEE T	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 11/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/972,744	BRUCHEZ ET AL.	
	Examiner	Art Unit	
	Pensee T. Do	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6, 11-20, 25-35, 38, 74-108* is/are pending in the application.

4a) Of the above claim(s) *16-20,25-35,38 and 80-108* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,11-14 and 74-79* is/are rejected.

7)☒ Claim(s) *15* is/are objected to.

8)☒ Claim(s) *1-6, 11-20, 25-35, 38, 74-108* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry & Claim Status

The amendment filed on May 19, 2005 has been acknowledged and entered.

Claims 1-6, 11-20, 25-38, 74-108 are pending.

Claims 16-20, 25-35, 38, 80-108 are withdrawn from further consideration.

Claims 1-6, 11-15, 74-79 are being examined.

Election/Restrictions

Newly submitted claims 80-108 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the composition of claims 80 and 96 are different from the present invention because they are unrelated to the composition of claim 1 for they contain different components such as a chip and a non-endogenous protein. The composition of claim 1 and the composition of claim 80 are not disclosed as capable of use together because they have different component, the composition of claim 80 requires to be immobilized on a chip while the composition of claim 1 does not require a chip. Thus, these compositions have different effects because the chip can be coded and conveniently used for detection. The composition of claim 1 and that of claim 96 are different because claim 96 requires the nanocrystal to be conjugated to a non-endogenous proteins and they are not required to be localized in the cytoplasm, nucleus or organelle of the cell. Thus they are not capable of use together and have different effects.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for

prosecution on the merits. Accordingly, claims 80-108 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Withdrawn Rejection(s)

Rejections under 112, 2nd paragraph are withdrawn herein.

Objection to the specification is also withdrawn herein.

Rejection under 102 (e) by Barbera-Guillem is withdrawn herein.

Maintained Rejection(s)

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3, 6, 11-14 are rejected under 35 U.S.C. 102(e) as being anticipated by Bawendi et al. (US 6,306,610).

Bawendi teaches a composition comprising fluorescent semiconductor nanocrystals associated to a molecule such as cells, prokaryotic or eukaryotic. The semiconductor nanocrystals comprise a CdSe core and a ZnS shell. The composition is also associated with cell membranes. (see col. 3, line 60-col. 4, line 62; col. 19, lines 58-60; col. 20, lines 51-59; col. 29, lines 41-42).

New Grounds of Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 4 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bawendi et al. (US 6,306,610).

Bawendi has been discussed above.

However, Bawendi fails to teach the cell is selected from the group of a yeast cell, mammalian cell such as human cell, mouse cell, rat cell, bovine cell and a hamster cell, and a plant cell.

Since Bawendi teaches eukaryotic cells (see col. 19, line 65), it would have been obvious to one of ordinary skills in the art to experiment cells such as yeast, mammalian cells of rat, mouse, bovine, hamster, and plant cell since it is well known that those cells are eukaryotic cells.

Claims 74 , 75 and 77are rejected under 35 U.S.C. 103(a) as being unpatentable over Bawendi et al. (US 6,306,610) in view of Rothbard et al. (US 6,306,993).

Bawendi has been discussed above. In addition, Bawendi teaches that the fluorescence semiconductor nanocrystals can associate with a molecule or reagent for

detection of a biological compounds such as enzymes, cellular organelles, cell membrane molecules involved in signal transduction and such composition can be used to detect cell morphology and fluid flow, cell viability, proliferation and function; endocytosis and exocytosis. (see col. 20, lines 50-60).

However, Bawendi fails to teach the nanoparticle is conjugated to a translocatable molecule and that the translocatable molecule is a ligand for a cellular receptor that enters the cell by endocytosis and that the translocatable molecule is a ligand for a transporter.

Rothbard teaches methods and composition for transporting drugs and macromolecules across biological membranes wherein the biological membranes are contacted with a conjugate containing a biologically active agent (ligand) that is covalently attached to a transport polymer (transporter). Such transport polymer has 6 to 25 subunits of L-Arginine. The transport enhancing polymers are exemplified by peptides in which arginine residues constitute the subunits. Exemplary eukaryotic cell membranes of interest include membranes of dendritic cells, epithelial cells, endothelial cells, keratinocytes, muscle cells, fungal cells, bacterial cells, plant cells and the like. Biological active agents are macromolecules such as nucleic acids, peptides, proteins and analogs thereof. The agent may be linked to the polymer by a linking moiety. The composition includes a conjugate containing a biological active agent covalently attached to at least one transport polymer and can be packaged with instructions for using it. (see col. 2, line 44-col. 4, line 45; col. 5, lines 47-58). The transport polymers contain short-length polymers from 6 to 25 subunits. The conjugate is effective to

enhance the transport rate of the conjugate across the biological membrane relative to the transport rate of the non-conjugate biological agent alone. (see col. 6, line 63-col. 7, line 5). Detecting uptake of macromolecules may be facilitated by attaching a fluorescent tag. (see col. 11, lines 3-4). Fluorescently labeled peptide polymers composed of 6 or more arginine residues entered cells more efficiently than the tat sequence 49-57 in fig. 1 (see col. 11, lines 30-40). Since the polymer of Rothbard composes of 6 to 25 contiguous Arg residues, it must be a cationic polymer.

Since Bawendi and Rothbard both teach using a label such as nanocrystals for cells or cell membrane, it would have been obvious to one of ordinary skills in the art to associate the polymer composition (comprising a ligand coupled to a transporter) taught by Rothbard to the nanocrystals as a fluorescent label and use in the composition of Bawendi because macromolecules such as peptides and oligonucleotides experience difficulty in passing across the biological membrane and having a polymer as a transportable molecule as that of Rothbard enhances trans-membrane transport. Furthermore, the nanocrystals of Bawendi can be used a label which associates with the polymer to so that measures of biological molecules transported across the biological membrane can be easily detected because the nanocrystals of Bawendi associates with the biological membrane. Regarding claim 75, since Bawendi teaches that the nanocrystal can couple to a reagent for detection of biological compounds, organelles and studying endocytosis, it would have been obvious to one of ordinary skills in the art that such "reagent for detection of biological compounds, organelles" is a ligand for a cellular receptor that enters the cell by endocytosis because in order to

study endocytosis, the cells must be labeled with the nanocrystal which in turn must be coupled to a ligand or a molecule that enters the cell membrane. It is well known that "endocytosis" is one of the methods for a compound to transport across the cell membrane.

Claim 76 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bawendi and Rothbard as applied to claim 74 above, and further in view of Sodroski et al. (US 6,761,902).

Bawendi and Rothbard have been discussed above.

However, both references fail to teach that the translocatable molecule is a ligand for a G-protein coupled receptor (GPCR).

Sodroski teaches that G-protein coupled receptors (GPCR), which span the membrane seven times. These are functionally linked to signaling proteins known as G-proteins. (see col. 8, lines 13-52).

Therefore, it would have been obvious to one of ordinary skills in the art to couple the transmembrane receptor GPCR as taught by Sodroski to the "reagent for detecting biological compound" to study the endocytosis and exocytosis or to encode the cell as taught by Bawendi and Rothbard because the transmembrane receptor GPCR can cross the cell membrane seven times. Thus, study of endocytosis or exocytosis can be effectively performed.

Claim 78 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bawendi et al. (US 6,306,610) in view of Frankel et al. (US 5,652, 152).

Bawendi has been discussed above.

However, Bawendi fails to teach that the translocatable molecule is a HIV-Tat protein.

Frankel teaches intracellular delivery of cargo molecules by the use of transport polypeptides which comprise HIV tat protein or one or more portions thereof and which are covalently attached to the cargo molecules. The transport polypeptides are characterized by the presence of the tat basic region (amino acids 49-57). The biological active cargo molecules such as polypeptides, nucleic acids are delivered/transported into the cytoplasm and nuclei of cells in vitro and in vivo. (see abstract). Label such as a fluorescent was used to study the transported molecules across the cell membrane. The label is attached to the tat peptide. (see col. 42, lines 24-29).

It would have been obvious to one of ordinary skills in the art to use the HIV tat peptide for transporting biological molecules across the cell membrane as taught by Frankel and attach it to a fluorescence semiconductor nanocrystal which associates to a cell membrane or a subcellular organelle so that when biological molecules to be transported reach the cell membrane, they can be transported effectively and efficiently with the aid of the tat peptide and their activity or measurement can be detected by the nanocrystals since the nanocrystals have a spectral emission that is tunable to a desired wavelength, and wherein said wavelength provides information about a biological state or event.

Claim 79 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bawendi in view of Barbera-Guillem (US 6,194,213).

Bawendi has been discussed above.

However, Bawendi fails to teach the composition further comprises a liposome.

Barbera-Guillem teaches a composition comprising functionalized nanocrystals and lipid membrane labeled such nanocrystals. Lipid membranes include cell membranes, liposomes, and lipid membrane-coated biosensors. (see col. 3, line 55-col. 4, line 20).

It would have been obvious to one of ordinary skills in the art to use liposomes as a lipid membrane as taught by Barbera-Guillem in the composition of Bawendi since both references teach using nanocrystal to label lipid membrane or cell membrane. Liposome is well known as a carrier or delivery vehicle for drugs, proteins, or other compounds. Thus, having a liposome as part of the composition of Bawendi can transport the nanoparticles across the cell membrane.

Response to Arguments

Applicant's arguments filed May 19, 2005 have been fully considered but they are not persuasive.

Regarding the 102 rejection by Bawendi, Applicants submit that Bawendi fails to disclose cells labeled intracellularly in the cytoplasm, nucleus, or an organelle. Also Applicants appear to argue methods, which are not relevant to the issues of the composition.

Bawendi teaches the use of a semiconductor nanocrystal associated with a compound that has affinity for a biological target including cells, subcellular organelles. (see col. 4, lines 56-65). Since subcellular organelles are located within the cytoplasm

of the cell, and the organelles are associated with the nanocrystal, the cytoplasm is inherently labeled with the nanocrystal associated with the organelles. Thus, Bawendi meets the requirement of claim 1.

Allowable Subject Matter

Claim 15 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pensee T. Do whose telephone number is 571-272-0819. The examiner can normally be reached on Monday-Friday, 7:00-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Pensee T. Do
Patent Examiner
October 28, 2005

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10/28/05